REMARKS

Reconsideration of this Application and entry of this Amendment is respectfully requested. By the amendments, the Applicant does not acquiesce to the propriety of any of the Examiner's rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

No new matter has been added as a result of the present amendments.

In the claims

Claims 1-6, 8-10 and 12-21 are currently pending in the application. Claims 10 and 12 are amended at the suggestion of the Examiner.

The amendments to claims 10 and 12 place the application in better condition for examination. It is submitted that no new matter has been introduced by these amendments, and they are fully supported by the specification as filed.

35 U.S.C. §112 Rejections

The Action rejects claims 1-10, 17, and 18 under 35 USC 112, first paragraph, as failing to comply with the written description requirement by containing "subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." *See* Office Action at p3. Specifically, the Action asserts that the amendments made to claim 1 in response to the Office Action of September 18, 2009, ("with a hollow bore" and "wherein the administration of said liquid solution comprising botulinum toxin does not follow the administration of a first drug within said session") are not supported by the claims as originally filed or the specification. *See* Office Action at p3.

Respectfully, in accordance with MPEP 2163(I)(B), it is pointed out that "there is no *in haec verba* requirement, thus newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." As previously explained, paragraph 44 is replete with U.S. Patents and Applications related to the botulinum toxin arts, and these are incorporated by reference into the instant disclosure.

These references provide ample support for the assertion that hollow bore needle administration of botulinum toxin was well known in the art to those of ordinary skill.

Nevertheless, with regard to "with a hollow bore," the Applicant respectfully points to paragraphs 26-39 of the specification as filed, all of which describe intramuscular injections of botulinum toxin. Statements including "[T]o reconstitute vacuum-dried BOTOX.RTM., sterile normal saline without a preservative; (0.9% Sodium Chloride Injection) is used by drawing up the proper amount of diluent in the appropriate size syringe" (paragraph 26), "about 75-125 units of BOTOX.RTM. per intramuscular injection" (paragraph 28), "about 30-80 units of BOTOX.RTM. to treat constipation by intrasphincter injection of the puborectalis muscle" (paragraph 30), and "to treat strabismus, extraocular muscles have been injected intramuscularly with between about 1-5 units of BOTOX.RTM" (paragraph 32) all clearly imply the use of hollow bore needles to one of ordinary skilled in the relevant art, as hollow bore needles have been used for years to deliver intramuscular injections. As stated above, by MPEP 2163(I)(B), newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. Regarding the instant application, the use of hollow bore needles is clearly implicit, and thus the 35 USC 112, first paragraph rejection as to "with a hollow bore" should be withdrawn.

With regard to "wherein the administration of said liquid solution comprising botulinum toxin does not follow the administration of a first drug within said session," the Applicant respectfully directs the Examiner to paragraph 108 of the application as-filed:

> Additionally, the present invention includes local administration methods to alleviate a skin disorder wherein two or more neurotoxins, such as two or more botulinum toxins, are administered concurrently or consecutively. For example, botulinum toxin type A can be administered until a loss of clinical response or neutralizing antibodies develop, followed by administration of botulinum toxin type B. Alternately, a combination of any two or more of the botulinum serotypes A-G can be locally administered to control the onset and duration of the desired therapeutic result. Furthermore, non-neurotoxin compounds can be administered prior to, concurrently with or subsequent to administration of the neurotoxin to proved adjunct effect such as enhanced or a more rapid onset of denervation before the neurotoxin, such as a botulinum toxin, begins to exert its therapeutic effect.

As quoted above, the Specification clearly delineates embodiments of the invention wherein administration of the neurotoxin can be preceded, accompanied, or followed by administration of other neurotoxins or, indeed, "non-neurotoxin compounds." Clearly "non-neurotoxin compounds" includes the "first drug" as specified in claim 1. By describing alternative embodiments such as those wherein administration of the neurotoxin can be preceded, accompanied, or followed by administration of other neurotoxins or non-neurotoxin compounds, the specification clearly implies embodiments wherein the administration of said liquid solution comprising botulinum toxin is not preceded, accompanied, or followed by administration of other neurotoxins or non-neurotoxin compounds. Indeed, each of the Examples in the instant specification describes protocols wherein the application of the botulinum toxin does not follow application of any other drug.

As stated above, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. Here, the specification clearly supports the referenced amendment under MPEP 2163(I)(B). Therefore, the Applicant requests that the Examiner withdraw the rejection under 35 USC 112, first paragraph as to "wherein the administration of said liquid solution comprising botulinum toxin does not follow the administration of a first drug within said session."

35 U.S.C. §103 Rejections

The Action rejects claims 12-16 and 19-21 under 35 USC § 103(a) as unpatentable over U.S. Patent Publication No. 2004/0087893 (Kwon) as evidenced by Allergan (pages 1-4 http://www.allergan.com/download/BotoxPI.pdf accessed on March 22, 2007), and further in view of What is Hyperkeratosis (Health A-Z www.everydayhealth.com; accessed 5/19/10) and Seborrheic Keratosis (eMedicine Dermatology www.emedicine.medscape.com; accessed 5/19/10). *See* Office Action at p4. Applicant respectfully disagrees.

To establish a *prima facie* case of obviousness under 35 U.S.C. §103, the Office must meet four conditions. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art itself

would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). As taught by *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

As amended, pending independent claim 12 recites a method for treating a typical mole, a dysplastic mole, a pyogenic granuloma or a seborrheic keratose by administering by intradermal injection or subdermal injection with a needle a therapeutically effective amount of a liquid solution comprising a botulinum toxin. In comparison, Kwon does not disclose a method for treating a typical mole, a dysplastic mole, a pyogenic granuloma or a seborrheic keratose by administering a therapeutically effective amount of a liquid solution comprising a botulinum toxin.

Turning to Kwon, the following material is quoted from the '893 publication, paragraph 25:

> In preparing an SSP perforator, a mold is prepared using precision machining, micro-machining (such as MEMS), or laser-based or electro-discharge machining. When the mold is prepared, a liquid solution, including the matrix material and including the selected drug(s), is cast in the mold and dried. To form a solid solution, the solvent needs to be air-dried, vacuum-dried or freeze-dried. Once a solid solution is formed, an SSP perforator is separated from the mold and cut to an appropriate shape and size.

Thus, to practice the invention of Kwon, the liquid phase drug of interest, along with the matrix material, is cast into a mold and dried to form the "solid drug solution perforator" (SSP), which is then applied to the skin of a patient such that the SSP penetrates the skin and then dissolves: "[F]or drug delivery, the SSP system includes an active drug ingredient and a matrix of perforator material that biodegrades or dissolves quickly upon contact with a patient's body." *See* Kwon abstract. Kwon mentions botulinum a single time (paragraph 74) in the context of vaccination. BOTOX® is also mentioned a single time, in the final paragraph (77) of the reference:

> Another area of applications is cosmeceutical. An SSP system including a patch can deliver botox toxin or a hydroxyacid more efficiently and safely to remove or reduce wrinkle formation and skin aging. The system is also useful for treating lesions or abnormal skin features, such as pimples, corns, warts, calluses, bunions, actinic keratoses and hard hyperkeratotic skin, which is often found on the face, arms, legs or feet. An SSP system is also useful as a food patch to deliver essential amino acids, fats and vitamins. A food patch is often used in emergencies.

Thus, Kwon discloses the application of BOTOX® via an SSP. As quoted previously, the SSP system "includes an active drug ingredient and a matrix of perforator material that biodegrades or dissolves quickly upon contact with a patient's body." The matrix of perforator material is cast from a mold containing "a liquid solution, including the matrix material and including the selected drug(s)" and then "air-dried, vacuum-dried or freeze-dried" to form the solid penetrator elements.

As a result, Kwon fails to disclose the injection of a liquid botulinum toxin solution, because the botulinum toxin solution hinted at by Kwon would apply the botulinum toxin solution as a solid, or at best a multi-phase substance that transitions from solid to liquid phase as it melts within the patient. Further, Kwon achieves drug delivery via penetrators made from "material that biodegrades or dissolves quickly upon contact with a patient's body." *See* Abstract. To sum, Kwon discloses the application of a dry, solid, BOTOX® substance mixed with some unknown biodegradable material to form a "penetrator" that can somehow deliver viable botulinum toxin intradermally to a patient.

This contrasts sharply with Claim 12's liquid botulinum toxin solution delivered by intradermal injection or subdermal injection with a needle, and so to bridge the gaps

between Kwon and the instant claims, the Examiner has cited Allergan BOTOX® product information (indicating that BOTOX® is botulinum toxin A) as well as two websites. Regardless, even if the combination of references were to render the rejected claims obvious , the combination itself is improper.

As stated previously, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). As taught by *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). Regarding the instant application, there is no such teaching, suggestion, or motivation. For example, as described in MPEP 2143.01(I), in *In re Fulton*, 391 F.3d 1195, 73 USPQ2d 1141 (Fed. Cir. 2004), the court stated that "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed" *Id.*

Here, in contrast to *Fulton*, the primary reference does in fact teach away from the needle injection of the claimed invention, such as in paragraph 4:

> Needle injection provokes needle phobia, substantial pain, local damage to the skin in many patients. Withdrawal of body fluids, such as blood, for diagnostic purposes provokes similar discomforts. Further, needle injection is not ideal for continuous delivery of a drug, or for continuous diagnosis.

Paragraph 7 of Kwon also teaches away from needle injections:

> Other attempts, such as particle or liquid injection, have been made to design alternative techniques to transfer drugs transdermally. A main advantage of those techniques is absence of needle use and reduction of incidence of contamination. However, liquid injection frequently causes some pain and/or sub-dermal hemorrhage. One technique, ballistic particle injection, is hard to administer exactly and continuously and can cause micro-bleeding.

Paragraph 12 of Kwon also teaches away from needle injection:

> In contrast to conventional hollow needle technologies, the SSP system includes a solid matrix of dissolvable (including meltable) or biodegradable

material that optionally holds one or more selected drugs and is formed into one or more perforators.

Because Kwon clearly teaches away from the claimed invention, Kwon is not suitable for combination with the other references cited in the Action's 35 U.S.C. §103 rejections.

Therefore, alone or in combination, the cited references fail to teach or suggest each element of the claimed invention. Accordingly, the Office has not established a *prima facie* case of obviousness and the Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

For the foregoing reasons, Applicant believes all the pending claims are in condition for allowance and a Notice of Allowance to that effect is respectfully requested. The Commissioner is hereby authorized to charge any additional fees which may be required for entry of this paper, or credit any overpayment, to Deposit Account No. 01-0885. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, the Examiner is kindly urged to call the undersigned at telephone number (714) 246-2842.

Respectfully submitted,

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